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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,348	07/13/2001	Avi Ashkenazi	10466/55	3826

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EXAMINER
SAOUD, CHRISTINE J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/905,348	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE f this communication appears on the cover sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 39-51 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 39-51 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Sequence Alignment

DETAILED ACTION

Status of the Claims

Claims 39-51 are pending in the instant application. Claims 1-38 have been canceled and claims 39-51 added as requested by Applicant in Paper #8, filed 13 July 2001.

Priority

Applicant has amended the priority claim in the first line of the specification in paper #9, filed 26 August 2002.

Specification

The disclosure is objected to because it contains embedded hyperlinks and/or other forms of browser-executable code. See at least page 147, line 32. The specification should be carefully reviewed for any other occurrences of hyperlinks. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Formal Matters

The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see MPEP Chapter 2400 and 37 C.F.R. § 1.801-1.809. Examiner acknowledges the deposit of organisms under accession number ATCC 209250 under terms of the Budapest Treaty on International

Recognition of the Deposit of Microorganisms for the Purposes of Patent procedure in compliance with this requirement (see the Specification at page 147).

Claim Rejections - 35 USC § 101

- 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 39-51 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Claims 39-44 are directed to an isolated protein of SEQ ID NO:4, identified as PRO232. The instant specification discloses that PRO232 is 114 amino acids long and has 35% sequence identity with a stem cell surface antigen from *Gallus gallus* (see page 150, lines 11-15 of the specification). However, the protein does not have any specific and substantial utility, or a well-established utility, as determined according to the current Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, January 5, 2001.

The claims are directed to isolated polypeptides having at least 80% sequence identity to the polypeptide of SEQ ID NO:18, with or without its signal peptide, or to the extracellular domain of SEQ ID NO:18 with or without its signal peptide. Dependent claims are directed to chimeric proteins comprising the aforementioned polypeptides. The specification contains numerous asserted utilities for the nucleic acid and polypeptide, including use as hybridization probes, in chromosome and gene mapping, in the generation of anti-sense RNA and DNA, to identify molecules that bind to PRO

(including agonists and antagonists), to make "knock-out" mice or other animals, in gene therapy, as molecular weight markers, therapeutic agents, and for the production of antibodies. The utilities that pertain solely to the nucleic acids (e.g. hybridization, chromosome and gene mapping, antisense therapy) would not convey to the encoded protein. With respect to the remaining utilities, none of these asserted utilities is specific for the disclosed PRO232 protein, as each of the aforementioned utilities could be asserted for any naturally occurring protein, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO 232.

The specification teaches that PRO232 has 35% sequence identity to a stem cell surface antigen from Gallus gallus. The specification at page 243-244 additionally indicates that PRO232 is not a stem cell marker, so the sequence identity does not appear to provide a specific and substantial utility for use as a marker to sort stem cells. The specification does not disclose any activity for the PRO232 protein, discloses no correlation to any disease or condition, and fails to provide any suggestion as to a biological function for PRO232. Page 244 of the specification speculates that the mRNA may serve as a marker for urethelial derived tissues, but this does not appear to be a substantial utility for the claimed invention.

The specification at pages 230-234 describes experiments in which PRO232 encoding genes are asserted to be amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. The specification further indicates that ΔCt is used as a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results

to normal human DNA results. The data regarding PRO232 may be applicable to claims directed to nucleic acid molecules, but an increase in copy number of the nucleic acid does not correlate to increased amounts of protein. Therefore, this data is not indicative of a use for the polypeptide as a diagnostic agent. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, Curr. Opin. Oncol. 12: 82-88, 2000). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not supported by analysis of mRNA or protein expression, for example. Also, it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that the encoded protein would be useful diagnostically or as a target for cancer drug development. For example, Pennica et al. (PNAS USA 95: 14717-14722, 1998) teach that

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced n the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See page 14722, second paragraph of left-hand column; pages 14720-14721, "Amplification and Aberrant Expression of *WISP*s in Human Colon Tumors".

Haynes et al. (Electrophoresis 19 : 1862-1871, 1998), studied 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript levels. For some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (page 1863, second paragraph, and Figure 1).

Thus, the data do not support the implicit assertion that the PRO232 polypeptide can be used as a cancer diagnostic. Additionally, there is no evidence of record which indicates that the encoded protein plays any role in tumor formation and/or growth. As seen above, increased mRNA does not correlate to increased protein, and therefore, one of ordinary skill in the art would not conclude a likelihood of the protein influencing tumor formation and/or growth. Significant further research is required of the skilled artisan to determine whether PRO232 is overexpressed in any cancer to the extent that antibodies to the protein could be used as a cancer diagnostic, or if the protein influences tumor formation and/or growth to the extent that it would be a therapeutic agent or target of therapeutic compounds, and thus the implicitly asserted utility is not substantial.

Claims 39-51 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

- The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858, F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:18 or the extracellular domain thereof, both referred to as PRO232. There is no functional limitation in the claims and no function is for the claimed protein is taught in the specification. The claims encompass an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. While the specification suggests that the polypeptide of SEQ ID NO:18 has some amino acid sequence identity to a stem cell surface antigen, no

function is attributed to this protein and it is not a marker for stem cells (page 244 of the specification). As opposed to the claims, what is disclosed about PRO232 is narrow: a single polypeptide with no disclosed function. The skill in the art does not make up for the deficiencies in the specification as to the function of the claimed protein. Therefore, knowledge of the amino acid sequence similarity to a stem cell surface antigen does not provide predictability about function of a structurally related protein since the specification has concluded that the protein does not serve as a marker for stem cells.

There are no working examples of polypeptides less than 100% identical to the polypeptide of SEQ ID NO:18 or the mature form thereof. There are no functions attributed to PRO232. The specification does not provide guidance for using polypeptide related to (i.e., 80%-99% identity) SEQ ID NO:18 because the specification fails to teach how to use the protein of SEQ ID NO:18. The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

For these reasons, which include the complexity and unpredictability of the nature of the invention and the lack of knowledge about the function(s) of encompassed polypeptides structurally related to PRO232 having the amino acid sequence of SEQ ID NO:18, the one example of PRO232, the lack of direction or guidance for using the polypeptide of SEQ ID NO:18 or polypeptides which are structurally related by amino acid sequence, and the breadth of the claims for structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

Claims 39-44 and 50-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95%, or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath In. v. Mahurkar, 19 USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for the purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the

encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to a lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:4, but not the full breadth of the claims meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

- The following is a quotation of the second paragraph of 35 U.S.C. 112:

  The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The protein identified as PRO232 appears to be a soluble protein, and is not disclosed as being expressed on a cell surface. Accordingly, the imitation that the claimed protein comprises an "extracellular domain" (for example, see claim 39, parts (c) and (d)) is indefinite, as the art does not recognize soluble proteins as having such domains. Further, if the protein had an extracellular domain, the recitation of "the extracellular domain" ... "lacking its associated signal sequence" (claim 39, part (d), for

example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

Priority Determination

As the claimed subject matter is found to lack utility and enablement under 35 U.S.C. §§ 101 and 112, first paragraph, respectively, the effective priority date for this application is the instant filing date, 13 July 2001.

Claim Rejections - 35 USC § 102

- The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

  A person shall be entitled to a patent unless –

  (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 39-44 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosenthal et al. (DE 19818619-A1, 28 October 1999).

Rosenthal et al. disclose a protein which has an amino acid sequence that is 95-98% identical to that of the claimed protein of SEQ ID NO:18 (SEQ ID NO:82 at page 111 and claim 23; sequence alignment is attached). The differences in the amino acid sequence are at the N-terminal portion of the protein, which would be in the "signal sequence" portion of the protein. Therefore, in addition to meeting the limitations for % identity, the protein of Rosenthal et al. also meets the claim limitations in which the signal sequence is missing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 703-305-7519. The examiner can normally be reached on mttr, 8:00-2:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud